

not put them at an unfair competitive advantage or adversely affect customer volume and tips. Future research on the role drinking establishments can play in reducing alcohol-related problems should continue to focus on comprehensive strategies including government regulation, establishment policies, and server behavior. □

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Increased Risk of Ectopic Pregnancy with Maternal Cigarette Smoking

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ABSTRACT

As part of a case-control study of ectopic pregnancy, we evaluated the potential etiologic role of cigarette smoking. Maternal cigarette smoking at the time of conception was associated with an increased risk of ectopic pregnancy with a dose-response relationship (adjusted odds ratios: 1.30 to 2.49). On the other hand, partner's smoking was not associated with ectopic pregnancy. The study provides a supplementary argument towards a causal effect of smoking in the development of ectopic pregnancy. (*Am J Public Health* 1991;81:199-201)

Introduction

During the past two decades, the incidence of ectopic pregnancy has doubled or tripled in many parts of the world.¹ It currently constitutes 1.2 to 1.4 percent of all reported pregnancies¹, and remains the leading cause of maternal death during the first trimester of pregnancy in industrial countries.² The main identified risk factors are pelvic inflammatory disease (PID) and sexually transmitted diseases (STDs), previous ectopic pregnancies, pelvic surgery, previous use of intrauterine device (IUD), and oral contraceptives and IUD use at the time of conception.¹ Several studies have shown a positive association with cigarette smoking.³⁻⁸ In most of them, smoking was not the primary hypothesis and the precise quantity of cigarette smoked was not investigated. Furthermore, some important confounding factors (e.g., STDs) were not taken into account.

As part of a case-control study of ectopic pregnancy, we further investigated the potential etiologic relationship between cigarette smoking, correcting for the above deficiencies wherever possible.

Methods

A case-control study was conducted during 1988 in seven large maternity hospitals in the Paris area (France). The cases were women ages 15-44 years, whose diagnosis had been confirmed by coelioscopy or laparotomy (n = 279). For each case, the first woman who delivered in the same center following the operation of the index-case was eligible as a control. When the woman selected as a control refused to be interviewed (n = 7), the woman immediately following who delivered in the same center was taken instead.

The interview collected standardized information on reproductive history, birth control practices history, sexual history, medical history including STDs and PID,

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TABLE 1—Risk of Ectopic Pregnancy Associated with Sociodemographic Characteristics

Variables	Controls (n = 279) Number/ Percent of exposed		Cases (n = 279) Number/ Percent of exposed		Crude Odds ratio (95% CI)
Maternal Age (years)					
<20	10	3.6	4	1.4	0.63 (0.18, 2.18)
20–24	47	16.8	30	10.8	1
25–29	114	40.9	80	28.7	1.10 (0.64, 1.89)
30–34	72	25.8	91	32.6	1.98 (1.14, 3.44)
35–40	28	10.0	55	19.7	3.08 (1.61, 5.87)
≥40	8	2.9	19	6.8	3.72 (1.45, 9.57)
Nationality					
French	188	67.4	183	65.6	1
Foreign	91	32.6	96	34.4	1.08 (0.76, 1.53)
Educational Level					
None	13	4.7	11	4.0	0.77 (0.34, 1.78)
Primary	45	16.2	44	15.8	0.89 (0.56, 1.43)
Secondary	151	53.9	165	59.0	1
Higher	70	25.2	59	21.2	0.77 (0.51, 1.16)
Single Woman					
No	254	91.0	253	90.7	1
Yes	25	9.0	26	9.3	1.04 (0.59, 1.86)

surgical history, conditions of conception and sociodemographic characteristics. Maternal cigarette smoking was assessed by the number of cigarettes smoked per day at the time of conception. Information about the main sexual partner included: number of cigarettes smoked per day, educational level, socio-occupational class, and number of STDs during the past six months. Odds ratios (OR) and 95% confidence interval (CI) were used to describe the association between ectopic pregnancy and smoking.⁹ Unconditional multiple logistic regression was performed to control for maternity hospital and to adjust for the confounding effects of other exposures.¹⁰ The proportion of cases that can be attributed to cigarette smoking was assessed by the adjusted population attributable fraction calculated with a formula given by Walter,¹¹ and adapted for multivariate settings by Bruzzi, *et al.*¹²

Results

The main sociodemographic characteristics of cases and controls were similar except for age (Table 1).

A higher proportion of cases (40.1 percent) than controls (29.7 percent) were smokers at the time of conception (OR = 1.64, 95% CI: 1.15, 2.33). Furthermore, when smoking was analyzed as a categorical variable, we observed a clear dose gradient relationship between cigarette smoking and ectopic pregnancy (Table 2) (OR = 1.21 to 1.64, trend tendency $p <$

0.05). Variables adjusted for in the logistic regression model included: age, appendectomy, prior ectopic pregnancy, prior tubal surgery, prior spontaneous abortion, previous use of IUD, PID, induced conception cycle, use of IUD, combined contraceptive pill or progestative micropill at the time of conception. Adjustment slightly increased the crude estimates (Table 2). On the other hand, there was no association with partner's smoking (OR = 0.82, 95% CI: 0.58, 1.16). Since the adjusted OR of the ectopic pregnancy association with cigarette smoking was 1.68 and the prevalence of smoking among the controls was 0.30, the adjusted population attributable fraction in our population was 17 percent.

Discussion

We found an increased risk of ectopic pregnancy in women who were smokers at the time of conception. This association is supported by the dose-response relationship observed even after adjustment for identified confounding variables. Conversely, no such association was found with partner's smoking, an association not previously investigated. These results seem to eliminate possible masked behavioral confounding factors and strengthen the argument that cigarette smoking was a true direct risk factor of ectopic pregnancy.

Several potential sources of bias must be considered. Since cases and controls had similar demographic characteristics

and since adjustment for the center was performed, selection bias is probably limited. However, recall bias which may have led to an overestimation of the risk, bias associated with the misclassification of the recent quitters (probably small according to Chow),⁷ and the confounding effects of unidentified risk factors cannot be totally excluded.

Our findings are consistent with six previous epidemiological studies which collected information on maternal smoking habits.^{3–8} Despite methodological differences, these studies all found a positive association. Chow, *et al.*,⁷ found a positive association between smoking at the time of conception and ectopic pregnancy (adjusted OR = 2.2), but failed to demonstrate a dose-response relationship. In the study of Handler, *et al.*,⁸ the estimated relative risk associated with smoking rose from 1.4 for a woman smoking fewer than 10 cigarettes per day to 5.0 for 30 or more cigarettes per day. In that study, however, smoking was assessed during pregnancy. Because the pregnancies of the controls were longer, these women had greater possibility than cases to stop smoking during pregnancy and this may have led to an overestimation of the relative risk.

Alterations of tubal motility and ciliary function following injections of nicotine have been demonstrated.¹³ Nicotine also delays blastocyst implantation and alters spacing of implantation sites¹⁴ in animals. The possible role of low estrogen-levels is advocated by some authors.¹⁵ Several findings support this hypothesis: women smokers have lower estrogen-levels than controls¹⁶ and tubal contractions are clearly under estrogenic control.¹⁷ Another explanation for the deleterious effect of smoking involves the reduced immunity in cigarette smokers.^{18,19} The altered immunity may affect the tubal response to inflammation, resulting in an increased frequency of PID.⁷ However, the association between smoking and PID has not yet been extensively explored in epidemiological studies.

Our observed population attributable fraction of nearly 20 percent indicates the public health importance of this association. If a factor is a causal agent of the disease, the reduction in the rate which would occur if exposure is prevented is equal to this proportion.¹¹

In conclusion, our study provides a supplementary argument for the existence of a causal link between cigarette smoking and ectopic pregnancy. Smoking is widespread among women in many countries. In some cases, the prevalence among young women is ever increasing.^{20,21} The

TABLE 2—Risk of Ectopic Pregnancy Associated with Cigarette Smoking

Variables	Controls (n = 279) Number/Percent of exposed		Cases (n = 279) Number/Percent of exposed		Crude Odds ratio (95% CI)	Adjusted* Odds ratio (95% CI)
Current Smoking† (woman)						
No	194	69.5	160	57.3	1	1
Yes	83	29.7	112	40.1	1.64 (1.15, 2.33)	1.68 (1.11, 2.55)
Unknown	2	0.8	7	2.6		
Number of Cigarettes/Day§ (woman)						
0	194	69.5	160	57.3	1	1
1–10	40	14.3	40	14.3	1.21 (0.75, 1.97)	1.30 (0.73, 2.32)
11–20	37	13.3	60	21.5	1.44 (1.24, 3.11)	1.95 (1.14, 3.34)
>20	6	2.1	12	4.3	1.64 (0.89, 6.60)	2.49 (0.79, 7.82)
Unknown	2	0.8	7	2.6		
Partner's Smoking						
No	120	43.0	130	46.6	1	
Yes	129	46.2	114	40.8	0.82 (0.58, 1.16)	
Unknown	30	10.8	35	12.6		
Number of Cigarettes/Day (partner)						
0	120	43.0	130	46.6	1	
1–10	39	14.0	36	12.9	0.85 (0.50, 1.43)	
11–20	73	26.2	62	22.2	0.78 (0.52, 1.19)	
>20	17	6.0	16	5.7	0.93 (0.42, 1.80)	
Unknown	30	10.8	35	12.6		

*Adjusted on maternity hospital, maternal age, appendectomy, prior EP, prior tubal surgery, prior spontaneous abortion, previous use of intrauterine device (IUD), pelvic inflammatory disease, induced conception cycle, use of combined estrogen/progestative pill, IUD and progestative micropill at the time of conception.

†Smoking status at the time of conception.

§When smoking (number of cigarettes/day) was modeled as a continuous variable, the OR associated with smoking $x + 1$ cigarettes/day versus smoking x cigarettes/day was 1.03 (1.01 – 1.05).

link between ectopic pregnancy and smoking should therefore be considered as a public health issue. □

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